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Commentary

New treatments for breast cancer: Breakthroughs for patient care or just steps in the right direction?

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'Anyone who isn't confused doesn't really understand the situation.'
Ed Murrow, 1969

Summary

Three areas of clinical research in breast cancer treatment led to news breaking presentations at the American Society of Clinical Oncology (ASCO) meeting, 1998, in Los Angeles. All three subjects represent important advances in cancer medicine.

Prevention: Two related drugs, tamoxifen and raloxifene, were found in placebo controlled trials to significantly reduce the incidence of breast cancer for women at increased risk of developing the disease. Patterns of relapse showed that the reduced rate of breast cancer was exclusively observed for tumors expressing estrogen receptors, while the rate of tumors classified as estrogen-receptor negative was similar for the treatment and the control groups. This may indicate that the observed reduction in breast cancer incidence is due to a treatment effect on occult disease rather than its prevention. We certainly have no adequate information on mortality prevention.

Adjuvant therapies: Taxol given every three weeks for four courses following an adjuvant treatment with four courses of doxorubicin and cyclophosphamide (AC) combination was found to be superior to not adding treatment after the four courses of AC in a trial involving 3170 patients. At 22 months of median follow-up, the quoted P-values were $P = 0.0077$ for disease-free survival and $P = 0.039$ for overall survival, but these did not cross the prospectively defined interim analysis boundaries for statistical significance at the 0.05 level. The difference was observed early during follow-up, and was exclusively seen in the 40% of patients who had ER-negative primaries and, therefore, did not receive tamoxifen following chemotherapy. One may thus argue that the early difference observed was primarily due to differences in the duration of the treatment regimens in the two groups and the early entry into the trial of patients with particularly aggressive neoplasia (e.g., ER-negative primaries) who would have benefited from a longer duration treatment.

Treatment of advanced disease: The use of monoclonal antibodies to c-erb-B2 was found to induce responses in metastatic breast cancer. Patients with tumors expressing c-erb-B2 responded to weekly infusions of this biological agent. It was particularly impressive that the response rate for patients receiving infusion of the monoclonal antibodies together with the cytotoxics was superior to that with chemotherapy alone in a randomized trial. It is important to note that only patients with tumors overexpressing c-erbB-2 (the overall incidence is about 20%) were tested. It must still be demonstrated that the effect of these monoclonal antibodies is indeed confined to cells overexpressing c-erbB-2. Treatment related cardiac toxicity remains a problem, and the effects of treatment in various subsets of patients need to be defined before starting investigations in the adjuvant setting, which is a clear further objective of this specific research.

The significant findings from clinical research opened several new questions, which must be answered before allowing them to be employed in routine patient care.

Key words: adjuvant paclitaxel, breast cancer, Herceptin®, prevention, Raloxifene, Tamoxifen

It was important for women, patients, researchers, and care providers from the oncologic community to have up-to-date results of recent developments in the treatment of breast cancer. Presentations at the annual meeting of the American Society of Clinical Oncology (ASCO) in mid-May, 1998, in Los Angeles served this purpose well. The rapid sequence of significant results from clinical research was also reported in the media, announcing 'breakthroughs' in the headlines and quoting more or less accurately the cautious presentation and commentary of the investigators. Impressed by the scientific value of the findings and excited by the opportunity they provide for a potential improvement in patient care, as well as by the opportunity to develop further clinical research, we decided to comment upon some of the findings publicly.

SERMs (selective estrogen receptor modulators) for the prevention of breast cancer

Several weeks and months ago tamoxifen and raloxifene, respectively, were announced to prevent breast cancer

[1, 2]. Tamoxifen was studied in 13,388 women who had an elevated risk of breast cancer and were randomized to receive the drug or placebo for the duration of five years. The results of the study appeared first in the lay press and on the Internet. A significant reduction in invasive and *in situ* breast cancer was observed, which motivated the Data Monitoring Committee for the BCPT Trial P-01 of the NSABP to advise that women participating in the trial be informed of the results. The investigators reported a reduced invasive breast cancer incidence of 45%, 85 cases in the tamoxifen group compared with 154 cases in the placebo group. At the ASCO meeting they reported that the difference between the two treatment arms was exclusively confined to the ER-positive tumors, while no significant difference was observed between the 34 tumors expressing no or low levels of estrogen receptor in the tamoxifen group compared to 28 in the placebo group.

Data on the raloxifene trial were also presented. Raloxifene was primarily studied for its estrogen-like activity on bone and lipid metabolism. A large placebo-controlled randomized trial was conducted in women 60 years old or older who had osteoporotic fracture or reduced bone mineral density. Its results have been published [3]. At the ASCO Meeting the breast cancer incidence was presented showing a significant reduction of (combined) invasive and *in situ* breast cancer [2]. Overall, there was a 58% reduction in risk. Also for raloxifene it was reported that the difference in incidence of breast cancer was entirely confined to the ER-positive (and PgR-positive) tumors, while the incidence of ER-negative malignancies was equal in the two treatment groups. We thus conclude, as did Dr. K. Osborne, in his elegant formal discussion, that the early differences observed in these two trials are likely to be the result of a treatment effect of the SERMs on subclinical existing cancer, considering their known efficacy in patients with ER-positive tumors. The decision of the NSABP to stop the trial and to offer tamoxifen to all patients randomized to the placebo seems justified by the predefined stopping rule, but may therefore compromise the trials' objective – to assess the preventive value of the drug. It is in fact unclear whether the patients who developed an excess of breast cancer in the placebo group could be 'rescued' by post diagnosis adjuvant tamoxifen therapy. Now, by receiving tamoxifen instead of placebo, their risk to develop endocrine-therapy-responsive tumors will diminish, while their risk to develop endocrine-therapy-nonresponsive tumors will remain unchanged. Their risk to have one of the tamoxifen-related side effects will increase. Long term results from the trial will become diluted by the treatment switch. This pivotal trial of the NSABP and the results from the raloxifene trial provide, however, a major stimulus for clinical research in the field to move further. While the IBIS (International Breast cancer Intervention Study) [4] and the Italian [5] trials might still allow a more efficient answer on the question of prevention and long-term effects, the NSABP announcement of further research comparing tamoxifen and raloxifene (the STAR trial) seems to be an obvious continuation. Another important line of clinical research in this field is the possible correlation between c-erbB-2 overexpression and resistance to tamoxifen.

Adjuvant systemic treatments

Another trial that reported early at the ASCO Meeting was the Intergroup Trial 0102 led by the CALGB [6]. This randomized trial used a 3 × 2 design to compare three doses of doxorubicin (60, 75 or 90 mg/m^2 by random allocation) plus cyclophosphamide (600 mg/m^2) given i.v. on day 1 every three weeks for four courses (AC ×4), and to compare Taxol (paclitaxel 175 mg/m^2 in a three-hour infusion every three weeks) for four courses following AC *versus* no additional chemotherapy. Thus, eight courses of adjuvant systemic treatment were compared with four courses of AC (with the same randomized dose intensity). The trial accrued 3170 patients and was reported despite a very short median follow-up of 22 months. The recurrence rate was reduced by 22% and the death rate by 26% (P = 0.0077 and P = 0.039, respectively), but the prospectively defined interim analysis boundaries for statistical significance at the 0.05 level were not crossed. The presented results are shown in Table 1.

Although the absolute differences in early follow up are small, they represent substantial proportional reductions in the risk of relapse and death. One of the conclusions formulated by Dr. I. C. Henderson, who presented the trial, was therefore that the result of this study demonstrated a significant improvement of adjuvant systemic treatments. While it is likely that the addition of taxanes to the adjuvant treatment armamentarium will improve outcome, this trial unfortunately confounded the addition of a new drug with total adjuvant therapy duration. The early benefits seen with Taxol were exclusively in patients with ER-negative tumors. These patients are more likely to benefit from the longer duration treatment [7]. They were presumably also more likely to enter this trial early during recruitment because they had a higher risk of relapse to justify the higher level of toxicity from both the increasing doses of doxorubicin and the addition of Taxol. In fact, the two trials showing convincing and significant improvement of treatment results as compared to 'classical' CMF were those comparing six courses of CMF to more toxic regimens of cyclophosphamide, anthracycline (either doxorubicin or epirubicin), and fluorouracil (either CAF or CEF) given on days 1 and 8 for six courses every four weeks [8, 9].

Table 1 DFS and OS percentages (± s.e.).

	AC	AC followed by Taxol	P-value
DFS at 18 months	86% ± 1.2%	90% ± 1.0%	0.0077
OS at 18 months	95% ± 0.7%	97% ± 0.6%	0.0390

Thus, the schedule and duration of adjuvant therapies may play an important role in treating high risk breast cancer [10], and it is important that future trials testing the combination of taxanes within such regimens maintain designs that do not suffer from further confounding factors.

The new biology (at last) shows efficacy against metastatic disease

Results of the two studies on the first therapy engineered to target a specific protein defect underlying the malignant progression of breast cancer were presented. The discovery of the amplification of the c-erbB-2 gene, a member of the epidermal growth factor receptor family, and the overexpression of its product led to the development of a recombinant, humanized monoclonal antibody targeted towards the extracellular domain of the receptor (Herceptin®). The use of this monoclonal antibody in 222 patients with metastatic breast cancer expressing c-erbB-2 was found to induce complete responses in six patients and partial responses in 25 patients (overall response rate (CR + PR) 31 of 222 = 14%; 95% CI: 10%, 19%) [11]. The median duration of response was 8.4 months. Adverse effects of the antibody included symptoms such as chills, fever and paleness in a large proportion of the patients, indicating the multisystemic reaction to the drug, probably related to cytokine release. Furthermore, reduction in cardiac ejection fraction was observed in 10 patients of whom six were symptomatic and nine had prior anthracyclines.

The other important report at the ASCO Meeting involved the results of a randomized trial using Herceptin® with doxorubicin-cyclophosphamide (AC) or paclitaxel (T) in 469 patients with metastatic breast cancer overexpressing c-erbB-2. AC was given as first chemotherapy, while paclitaxel was used if the patients had received prior adjuvant doxorubicin [12]. The trial was based upon previous investigations *in vitro*, reported by the group of Dr. Slamon, describing a phenomenon called receptor-enhanced chemosensitivity, which, they predicted, may provide a rationale for more selective targeting and exploitation of overexpressed growth factor receptors in cancer cells [13]. Treatment regimens included the following doses of drugs and schedules: A = 60 mg/m^2, C = 600 mg/m^2, T = 175 mg/m^2 in a three-hour infusion, all given every three weeks for six courses. Herceptin® was given to half of the patients by random allocation (4 mg/kg loading, then 2 mg/kg i.v., once weekly). The results are summarized in Table 2.

Cardiac toxicity was also reported to be frequent in this trial, especially in the group receiving AC and Herceptin® (18% of grade 3 and 4). However, the improvement in treatment outcome was so impressive that it might justify evaluation of the combined regimen (chemotherapy and Herceptin®) in the adjuvant setting, though perhaps initially only for women at very high-risk of relapse, whose tumors contain some cells staining for c-erbB-2. Another important step is to further define the target population, which might benefit from the addition of Herceptin to chemotherapy. It is, therefore, essential to verify the degree of overexpression of c-erbB-2 needed to observe response. Further understanding of the clinical relevance and the pathophysiological background for the observed myocardial toxicity may be a *conditio sine qua non* for a reasonable continuation of investigations in the adjuvant setting.

Table 2. Treatment results with and without Herceptin®.

	AC + H	T + H	AC	T
ORR %	52	42	43	16
MRD mos.	9.1	11	6.5	4.4
TTP mos.	7.6		4.6	

Abbreviations: AC – doxorubicin-cyclophosphamide; T – paclitaxel; H – Herceptin®; ORR – overall response rate; MRD – median response duration; TTP – median time to progression.

It is rare that a Yearly Meeting provides so much new information with the potential to substantially influence patient care and future clinical research. This was the primary reason for summarizing our perception of its relevance.

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